

Letters to the Editor

Oxidative stress in the development of diabetes during hyperthyroidism

Sir,

Elevated fasting plasma glucose levels and impaired glucose tolerance are commonly observed as the most significant consequences of thyrotoxicosis. The prevalence of clinical diabetes mellitus is also increased in thyrotoxicosis.¹ The diabetogenic effect of increased levels of thyroid hormones has variously been attributed to an increased rate of glucose absorption from the gastrointestinal tract, a decreased in the ability of the liver to store glucose as glycogen, increased liver glycconeogenesis, impaired release of pancreatic insulin, and to increased peripheral insulin resistance, as well as to a decreased plasma insulin half-life.²⁻⁴ Some reports have linked both hyperthyroidism and diabetes mellitus with underlying autoimmune mechanisms rendering cells more susceptible to damage.⁵ The development of diabetes mellitus during hyperthyroidism leads to an aggravation of both diseases, potentiates the development of complications such as ketoacidosis, and may result in increased daily insulin requirements.¹ We report a patient who developed diabetes mellitus during hyperthyroidism, and suggest that increased oxidative stress during hyperthyroidism may be one of the pathogenetic abnormalities responsible for the development of diabetes.

Hyperthyroidism (toxic adenoma) was first diagnosed in a 35-year old man at our hospital. The diagnosis was based on clinical evaluation, ultrasound scanning, and the following laboratory values: serum thyroxine 187.5 nmol/l (reference range 55-165 nmol/l), tri-iodothyronine 3.2 nmol/l (1.2-2.5), thyroid-stimulating hormone 0.12 mU/l (0.17-4.5 mU/l). He was prescribed propylthiouracil at a daily dose of 200 mg. Six months later he developed diabetes mellitus. On admission after a further six months, he had poorly controlled diabetes mellitus with a fasting glucose level of 10.9 mmol/l while taking large doses of insulin (64 U/24 h in two daily doses). He also had an increased plasma fructosamine level of 0.78 U/g protein (0.35-0.45 U/g), while levels of fasting plasma triglycerides level (2.76 mmol/l), cholesterol (6.7 mmol/l) and LDL cholesterol (4.7 mmol/l) were slightly increased. The level of circulating immune complexes was almost double reference values (25.4 U/l vs 6-15 U/l), while plasma lipid peroxidation products were increased almost four-fold (38.72 µmol/l vs 6-12 µmol/l). The total plasma anti-oxidative capacity was decreased (64.6% vs 76-88% of control range), as was the level of reduced blood glutathione-GSH (0.70 µmol/ml vs 1.0-1.35 mol/ml).

It was particularly interesting that the hyperthyroidism was accompanied by a significant elevation in the plasma concentration of lipid peroxidation products. It has recently been reported that the levels of free radicals are increased in thyrotoxicosis, as a result of excessive mitochondrial oxygen consumption as well as an increase in the activity of xanthine oxidase.⁶ Free oxygen radicals produced under conditions of increased oxidative stress are capable of decreasing insulin

sensitivity and peripheral insulin effectivity, as they are capable of interacting with the insulin-messenger system of NO-guanylate cyclase-cGMP.⁷ Glucose tolerance is dependent on the interaction of tissue sensitivity to insulin and the magnitude of pancreatic insulin secretion. Enhanced production of free oxygen radicals may also cause damage to β-cells, leading to decreased secretory potential of islet cells, which have very low free-radical scavenging enzyme activity.^{8,9}

These observations suggest that increased oxidative stress during hyperthyroidism is capable of promoting the onset of diabetes mellitus, favouring peripheral insulin resistance and exhaustion of β-cells. This finding could be of pathophysiological importance, not only in explaining some of the basic mechanisms behind the development of impaired glucose tolerance and diabetes during hyperthyroidism, but also in providing a rationale for the use of anti-oxidative drugs at the onset of hyperthyroidism, to prevent or decelerate the development of impaired glucose tolerance and diabetes.

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Methotrexate pneumonitis precipitated by NSAIDs - can fish oil help?

Sir,

We read with interest the article of Clearkin *et al* describing a case of methotrexate pneumonitis presumably precipitated by concomitant use of diclofenac.¹ Low-dose methotrexate has become a second-line treatment for patients with rheumatoid

arthritis. Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently co-administered, notwithstanding the fact that such treatment in some cases leads to fatal aggravation of methotrexate toxicity. The mechanism of this is uncertain and may include either displacement of methotrexate from protein-binding sites, or an effect of NSAIDs on the kidney resulting in reduced methotrexate excretion, or both. Conflicting results have been reported with regard to safety of use of ketoprofen and naproxen with methotrexate,^{2,3} while it has been reported that flurbiprofen or piroxicam in clinically relevant doses do not affect methotrexate disposition in patients receiving low-dose methotrexate.³

Fish oil supplements have been found to reduce the need for NSAIDs in rheumatoid arthritis. Fish oils are rich sources of polyunsaturated fatty acids of the omega-3 series. Diets rich in omega-3 fatty acids appear to reduce inflammatory and immune response. Fish oils may be used in doses of 1-2 g daily without adverse effects.⁴ Encouraging results have also been reported on the beneficial effect of fish oils in diseases such as IgA nephropathy. We speculate that in systemic lupus erythematosus (which is also an extra-articular manifestation of rheumatoid arthritis), fish oils may be beneficial. Clinical studies investigating the effects of fish oils in the prevention and treatment of cardiovascular diseases are beginning to emerge⁵; it is likely that they can minimise the cardiovascular manifestation of rheumatoid arthritis.

We therefore suggest that, in patients with rheumatoid arthritis on low dose methotrexate who require NSAIDs, flurbiprofen or piroxicam may be preferred; further, the addition of fish oil supplements to this regimen may effectively reduce the dose of NSAIDs required and thereby minimise the adverse effects of methotrexate, including pneumonitis. This regimen may also have a beneficial effect on many of the extra-articular manifestations of rheumatoid arthritis. Hence, we feel that a modified therapeutic regimen of low-dose methotrexate and low-dose flurbiprofen/piroxicam with fish oil supplementation, deserves a trial in rheumatoid arthritis.

Fish oil has constraints like higher cost and contains cholesterol. Therefore, alternate vegetable sources of omega-3 fatty acids, such as walnuts, wheat germ soyabean lecithin, tofu, common beans, butternuts and seaweed, all of which are cost-effective and without cholesterol,⁶ could also be included in such a trial.

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